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(54) Title: METHODS AND COMPOSITIONS FOR TREATING HYPERTENSION, ANGINA, AND OTHER DISORDERS USING OPTICALLY PURE S(-) FELODIPINE (57) Abstract Methods and compositions are disclosed utilizing the optically pure S(-) isomer of felodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the racemic mixture of felodipine. The S(-) isomer of felodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of S(-) felodipine as a calcium channel antagonist such as cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, coronary vasospasm, myocardial infarction, renal impairment and acute renal failure, without the concomitant liability of adverse effects associated with the administration of the racemic mixture of felodipine.		

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METHODS AND COMPOSITIONS FOR TREATING
HYPERTENSION, ANGINA, AND OTHER
DISORDERS USING OPTICALLY PURE S(-) FELODIPINE

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1. BACKGROUND OF THE INVENTION

This invention relates to novel compositions of matter containing optically pure S(-) felodipine. These compositions possess potent activity in treating both systolic and diastolic hypertension while
10 avoiding adverse effects including but not limited to edema of the extremities, headache and dizziness, which are associated with administration of the racemic mixture of felodipine. Additionally, these novel compositions of matter containing optically pure
15 S(-) felodipine are useful in treating angina and such other conditions as may be related to the activity of S(-) felodipine as a calcium channel antagonist, including but not limited to cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy,
20 coronary vasospasm, myocardial infarction, renal impairment and acute renal failure, while avoiding the adverse effects associated with administration of the racemic mixture of felodipine. Also disclosed are methods for treating the above-described conditions in
25 a human while avoiding the adverse effects that are associated with the racemic mixture of felodipine, by administering the S(-) isomer of felodipine to said human.

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1.1. Steric Relationship and Drug Action

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R
35 and S are used to denote the absolute configuration of

the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is
5 levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an
10 enantiomer, and a mixture of such isomers is often called an enantiomeric or racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals, where 12 of the 20 most prescribed drugs exhibit chirality. A case in point
15 is provided by the L-form of the β -adrenergic blocking agent, propranolol, which is known to be 100 times more potent than the D-enantiomer.

Furthermore, optical purity is important since certain isomers may actually be deleterious
20 rather than simply inert. For example, it has been suggested that the D-enantiomer of thalidomide was a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, while the corresponding L-enantiomer has been thought to be
25 a potent teratogen.

The active compound of this composition and method is an optical isomer of the compound felodipine, which is described in Berntsson et al., United States Patent No. 4,264,611. Chemically, this
30 S(-) isomer is ethyl methyl 4-(2,3-dichlorophenyl)-1, -4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. This isomer will hereinafter be referred to as S(-) felodipine. S(-) Felodipine includes the optically pure and the substantially optically pure S(-)
35 felodipine isomer.

Felodipine, which is the subject of the present invention, is available commercially only as the 1:1 racemic mixture. That is, it is available only as the 1:1 mixture of optical isomers, called
5 enantiomers.

1.2. Pharmacologic Action

The racemic mixture of felodipine is in the class of compounds known as calcium antagonists or
10 calcium channel blockers. The concept of a specific mechanism of pharmacologic action related to the antagonism of calcium movement in the process of excitation-contraction was suggested by Fleckenstein
et. al. (see Fleckenstein, A., *Calcium Antagonism in*
15 *Heart and Smooth Muscle: Experimental Facts and Therapeutic Prospects*, New York, Wiley, 1983; Swamy, V. and Triggle, D., *Modern Pharmacology*, 2nd. Ed., Craig and Stitzel, Eds., Little, Brown and Co., Boston, 1986, Chapt. 26, pages 373-380; Triggle, D.J.,
20 and Janis, R.A., *Ann. Rev. Pharm. and Tox.* 27: 347-369, 1987). Many of the currently available calcium antagonists appear to antagonize the entry of calcium through voltage dependent channels in the plasma membrane of cells.

25 The pharmacologic class of calcium antagonists consists of three main chemical types; phenylalkylamines (e.g., verapamil), benzothiazepines (e.g. diltiazem), and 1,4-dihydropyridines (e.g. nifedipine). Given the structural heterogeneity
30 of the class it is likely that the pharmacological action involves more than one site or mechanism of action.

Nifedipine, the first commercially available 1,4-dihydropyridine, is achiral and therefore cannot
35 exist in optically active forms. Several second-

generation 1,4-dihydropyridines have been produced that are chiral, existing as R or S enantiomers (or alternatively, (+) or (-)). These include amlodipine, nicardipene, nimodipine, nitrendipine, isradipine, felodipine, nisoldipine and nilvadipine. The enantiomers of each of these compounds have been shown to have very different biological activities both in vitro and in vivo. Despite the fact that each enantiomer is pharmacologically distinct, all of the commercially available preparations of these compounds are racemic mixtures.

The enantiomers of felodipine have different pharmacokinetic and pharmacodynamic properties. In one study, a racemic mixture of felodipine was given orally to healthy human subjects. The R(+) isomer of felodipine was found to have a 2.4-fold higher clearance than the S(-) isomer, with the S(-) isomer exhibiting a 2.1-fold higher maximum plasma concentration; the terminal half-lives of the two enantiomers were comparable (Soons, P.A., *et al.*, *J. Chromat.*, 528: 343-356, 1990). This difference indicates stereoselective oxidation of the 1,4-dihydropyridine to its corresponding pyridine metabolite. This oxidation takes place in the liver, leading to the pharmacologically inactive pyridine (Edgar, B., *et al.*, *Biopharmaceutics & Drug Disposition*, 8: 235-248, 1987; Baarnhielm, C., *et al.*, *Xenobiotica*, 14: 719-726, 1984).

A study by Eriksson *et al.* reported that the pharmacokinetic parameters of the enantiomers of felodipine in dogs were similar after i.v. administration, indicating that the disposition of felodipine was not stereoselective (Ericksson, U.G. *Xenobiotica* 21(1): 75-84 (1991).

- 5 -

The S(-) isomer of felodipine was disclosed to be more potent than the R(+) isomer in in vitro studies. A study was made of each enantiomer's ability to inhibit coronary vasoconstriction of guinea pig Langendorff hearts induced by a thromboxane mimic. S(-) Felodipine was determined to be 13 times more potent than R(+) felodipine in this in vitro assay. The competitive binding of the enantiomers to guinea pig skeletal muscles was also examined. Each isomer competed for binding sites with radiolabelled isradipine, another 1,4-dihydropyridine. S(-) Felodipine was found to compete 12 times more effectively than R(+) felodipine for these binding sites. An in vivo study with spontaneously hypertensive rats showed that S(-) felodipine was 13 times more potent in lowering blood pressure (Eltze, M. et al., Chirality 2: 233-240, 1990).

The racemic mixture of felodipine is presently used primarily as an antihypertensive agent and is generally taken orally. As stated above, the racemic mixture of felodipine produces peripheral vasodilation, resulting in decreases in both systolic and diastolic blood pressure when used as an antihypertensive agent. This antihypertensive effect occurs in the relative absence of significant or sustained effects on cardiac rate.

While yet the subject of extensive research, hypertension appears to be the product of an inherited predisposition -- coupled with dietary, emotional, and environmental factors, which results in a structural adaptation of the cardiac muscle and the large blood vessels. Most patients display heightened vascular and cardiac reactions to sympathetic nervous stimulation, but the precise relationship of sympathetic nervous stimulation to the etiology of the

disease has yet to be determined. Nevertheless, hypertension results in chronic readjustment of cardiovascular hemodynamics, alteration of blood vessel walls, cardiovascular resistance and regional transmurals pressures.

Pharmacologic management of hypertension is generally directed to the normalization of altered hemodynamic parameters, and many drugs and drug classes, either as monotherapy or in combination treatment, can reduce and control elevated blood pressure. However, treatment of hypertension does not always correspondingly benefit the morbidity and mortality of the condition, either because chronic hypertension has produced other significant and irreversible cardiovascular changes, or because present drugs have an adverse effect on some other risk factor for cardiovascular disease. Rather, current drug therapy simply provides sustained arterial pressure reduction.

Furthermore, the racemic mixture of felodipine is useful in treating other disorders such as angina pectoris.

Angina pectoris is a highly variable, rather poorly understood clinical syndrome reflecting a myocardial ischemia. When cardiac work or myocardial oxygen demand exceeds the ability of the coronary arterial vascular system to supply oxygen, the resulting ischemia stimulates the sensory nerves of the heart, producing the sensation of angina characterized by episodes of precordial pressure, discomfort, or a severe, intense crushing pain which may radiate to several sites including the left shoulder and left arm. Physical activity or exertion characteristically initiates the condition, and rest or drug therapy relieves the condition. The signs and

- 7 -

symptoms of an episode persist for a few minutes, but can be induced or exaggerated by a meal or exposure to cold air. Treatment is directed to the underlying disease, usually atherosclerosis, or to drugs which
5 either reduce myocardial oxygen demand or improve oxygen supply. Calcium antagonists such as felodipine have been particularly useful in treating vasospastic angina, the angina of effort, and the unstable angina, due to the effect of the calcium channel antagonist on
10 cardiac and vascular smooth muscle.

Racemic felodipine may be useful in the treatment of cerebral ischemia. Cerebral ischemia, often the result of atherosclerotic disease or hypertension, results from insufficient cerebral
15 circulation. Under normal circumstances, an extensive collateral circulation ensures adequate blood flow. However, cerebral ischemia may result from either an intra- or extracranial interruption of arterial blood flow. If interruption is transient, the cerebral
20 tissues recover, and neurologic symptoms disappear. If the ischemia lasts for a somewhat more extended period, infarction results and the resulting neurologic damage is permanent. In the case of extended ischemia resulting in infarction, treatment
25 is directed to the underlying vascular disease, to blood platelet aggregation inhibitors, and anticoagulant therapy.

Because of its activity as a calcium channel antagonist, racemic felodipine may also be useful in
30 treating cardiac arrhythmias. Cardiac arrhythmias represent a broad, complex group of electrophysiologic disorders that affect the mechanical properties of the heart and vasculature, altering normal cardiac rhythm, function and output. Normal cardiac rhythm originates
35 with the sinoatrial node, which possesses high

- 8 -

intrinsic automaticity. Adequate automaticity and conduction lead to activation of atrial and ventricular fibers, producing in sequence the elements of normal functional heart beat. Calcium antagonists
5 may be of value in conditions where calcium-related changes in membrane potential and conduction alter normal rhythm. In the absence of treatment, symptoms vary with individual arrhythmias, but are often the consequence of inadequate cardiac filling and output
10 and often include fatigue, decreased exercise tolerance, syncope, shortness of breath, nausea, lightheadedness and the like.

Racemic felodipine may be useful to treat cardiac hypertrophy. Cardiac hypertrophy can result
15 from excessive workload either due to an obstruction to outflow, termed systolic overload, or to excessive volumes presented to the heart in diastole, termed diastolic overload. Systolic overload results in concentric ventricular hypertrophy, in which there is
20 an increased thickness in the walls of the heart not associated with increased volume. Diastolic overload causes dilation and hypertrophy with an increased blood volume. An inadequate cardiac output results from the heart's failure in systolic or diastolic
25 overload, leading to fatigue, shortness of breath, pulmonary congestion, edema and the like. Calcium channel antagonists effect workload and, as such, may be useful in treating cardiac hypertrophy due to the effect of the calcium antagonist on cardiac and
30 vascular smooth muscle in reducing blood pressure.

It is also possible that racemic felodipine could be used to treat coronary arterial spasm. Coronary arterial spasm can occur in the absence of significant coronary atherosclerosis and is thought to
35 be an initiating event in variant angina and in

- 9 -

myocardial infarction. Coronary spasm may occur without the patient feeling any significant discomfort. In an electrically unstable heart, diverse neural impulses to the heart may provoke

5 coronary vascular spasm. This may result in enhanced myocardial ischemia and arrhythmia, which in turn may culminate in ventricular fibrillation and sudden cardiac death. As in variant or vasospastic angina, the calcium channel antagonists may be of particular

10 usefulness due to their effect on cardiac and vascular smooth muscle.

Furthermore, racemic felodipine may be useful in the treatment of myocardial infarction, ischemic myocardial necrosis, and ischemia reperfusion

15 injury. Myocardial infarction or ischemic myocardial necrosis generally results from the abrupt reduction of coronary blood flow to a portion of the myocardium. The condition likely originates from atherosclerosis of the coronary arteries. Either coronary artery

20 vasospasm or acute coronary thrombosis precipitates the condition, although the etiology is the subject of continuing research. Myocardial infarction is predominantly a disease of the left ventricle. Precordial pain and left ventricular dysfunction

25 characterize the disease. The pain, which can be severe aching or pressure, leads to apprehension. Symptoms include left ventricular heart failure, pulmonary edema, shock or significant cardiac arrhythmia. Calcium channel antagonists may find

30 utility in the management of myocardial infarction patients due to their effects on coronary artery vasospasm, blood pressure or other effects on cardiac function or vascular smooth muscle.

Racemic felodipine may be used to treat

35 congestive heart failure. Congestive heart failure

- 10 -

can be caused by hypertension, cardiomyopathy, coronary artery disease or valvular heart disease. Congestive failure results in poor cardiac output and elevated left-ventricular diastolic pressure, leading to dyspnea, fatigue, peripheral edema, and coughing. The ability of some calcium antagonists to lower afterload by dilating peripheral arteries without having a significant inotropic effect may increase their use in treating congestive heart failure.

10 Racemic felodipine may also be of use in treating migraine. Classic migraine typically begins with visual auras followed by severe headaches, often accompanied by nausea and vomiting. Common migraine has similar symptoms without the preceding visual
15 aura. The causes of migraine have been studied intensely, and are still a matter of debate. The most generally accepted cause is hypoxia due to reduced cerebral blood flow. Calcium channel antagonists have been used for migraine prophylaxis since they can
20 increase cerebral blood flow.

In addition, racemic felodipine may be useful for treating Raynaud's phenomenon, which is characterized by vascular spasm of the extremities. These vasospasms can be caused by cold or stress. A
25 pallor or cyanosis is usually present due to severe constriction of the digital arteries. The phenomenon is often seen as a secondary disorder with arterial diseases or connective tissue diseases such as scleroderma, arthritis or lupus erythematosus.
30 Calcium channel antagonists have been shown to be effective in treating Raynaud's phenomenon.

Racemic felodipine may be useful in the treatment of asthma and bronchospasm. Symptoms of asthma - coughing, wheezing, and dyspnea - are caused
35 by constriction of tracheobronchial smooth muscle.

- 11 -

Asthma attacks can be triggered by antigenic stimuli (pollen, dust) or non-antigenic stimuli (exercise, pollution, infection). The response to these stimuli lead to secretions of chemical mediators that cause smooth muscle contraction. Calcium channel antagonists can be used to control bronchoconstriction and relieve asthma attacks.

In addition, the racemic mixture of felodipine may be useful to treat renal impairment and acute renal failure. Renal impairment and acute renal failure are clinical conditions of diverse etiology, which are associated with an increasing azotemia or urea nitrogen in the blood, and often an oliguria or a diminished volume of urine in relation to fluid intake. The pathophysiology may originate prerenally, manifest as inadequate renal perfusion, due to extracellular fluid volume depletion or cardiac failure. The most common cause of intrinsic renal failure is prolonged renal ischemia. Postrenal azotemia may be associated with obstruction or renal glomerular and tubular dysfunction. Laboratory findings disclose progressive azotemia, acidosis, hyperkalemia, and hyponatremia. Factors aggravating kidney impairment or failure must be specifically treated, including heart failure, obstruction and the like. Moderate or severe hypertension has a deleterious effect on renal function, and management of the hypertension with a variety of drugs including calcium channel antagonists may be useful therapy.

In addition, the racemic mixture of felodipine could be useful in the treatment of cognitive disorders. Cognitive disorders include but are not limited to dementia and age-associated memory impairment.

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- 12 -

Dementia can occur at any age. It is a structurally caused permanent or progressive decline in several dimensions of intellectual function that interferes substantially with individual normal social or economic activity.

One particular type of dementia is Alzheimers-type dementia. Alzheimers-type of dementia is thought to be due to a degenerative process, with a large loss of cells from the cerebral cortex and other brain areas. Acetylcholine-transmitting neurons and their target nerve cells are particularly affected. The brain shows marked atrophy with wide sulci and dilated ventricles. Senile plaques and neurofibrillary tangles are present. Memory loss is the most prominent early symptom. Disturbances of arousal do not occur early in the course. Alzheimer's presenile and senile onset dementias are similar in both clinical and pathologic features, with the former commonly beginning in the 5th and 6th decades and the latter in the 7th and 8th decades. The dementia usually progresses steadily, becoming well advanced in 2 to 3 years. Some cases of dementia occurring in the presenile period are hard to classify and are sometimes labelled idiopathic or simple presenile dementia.

The signs and symptoms of dementia in particular Alzheimers-type dementia include depression, paranoia, anxiety or any of several other psychologic symptoms. The most common clinical picture is slow disintegration of personality and intellect due to impaired insight and judgment and loss of affect. Memory impairment increases, beginning with problems recalling recent events or finding names. The impairment varies greatly from time to time and often from moment to moment.

Dementia generally is an insidious, slowly progressive, untreatable condition. However, the rate of progression varies widely and depends on the cause.

Another type of cognitive disorder is age-associated memory impairment (AAMI). AAMI is used to describe healthy non-demented people who have experienced memory loss over the course of the person's life. Most commonly it is used to describe adults over the age of 50 who have experienced memory loss over the course of adult life. It has been estimated that between 25% and 50% of people over the age of 65 have this disorder.

Many calcium channel antagonists cause significant adverse effects. These adverse effects include but are not limited to tachycardia, orthostatic hypotension and fluid retention.

In addition, the administration of the racemic mixture of felodipine to a human has been found to cause still other adverse effects. These adverse effects include but are not limited to edema of the extremities including peripheral edema, headache, flushing/hot flashes, fatigue, vertigo, muscle cramps and dizziness.

Thus, it would be particularly desirable to find a compound with the advantages of the racemic mixture of felodipine which would not have the aforementioned disadvantages of significant adverse side effects and which was useful for treatment of other conditions.

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2. SUMMARY OF THE INVENTION

It has now been disclosed that the optically pure S(-) isomer of felodipine is an effective antihypertensive agent for both systolic and diastolic hypertension, particularly in mild to

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- 14 -

moderate disease, and angina, while avoiding adverse effects including but not limited to edema of the extremities, headache and dizziness, which are associated with the administration of the racemic mixture of felodipine. It has also been discovered that these novel compositions of matter containing optically pure S(-) felodipine are useful in treating other conditions as may be related to the activity of S(-) felodipine as a calcium channel antagonist, including but not limited to cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, coronary vasospasm, myocardial infarction, renal impairment and acute renal failure while avoiding the adverse effects associated with the administration of the racemic mixture of felodipine. The present invention also includes methods for treating the above-described conditions in a human while avoiding the adverse effects that are associated with the racemic mixture of felodipine by administering the S(-) isomer of felodipine to said human.

3. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating hypertension in a human, while avoiding the concomitant liability of adverse effects associated with that administration of racemic felodipine, which comprises administering to said human in need of such antihypertensive therapy, an amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said hypertension, but insufficient to cause said adverse effects associated with administration of racemic felodipine.

The present invention also encompasses an antihypertensive composition for the treatment of a human in need of antihypertensive therapy, which comprises an amount of S(-) felodipine or a
5 pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said hypertension but insufficient to cause adverse effects associated with the administration of racemic felodipine.

10 The present invention further encompasses a method of treating angina in a human, while avoiding the concomitant liability of adverse effects, which comprises administering to said human in need of such anti-angina therapy, an amount of S(-) felodipine, or
15 a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said angina but insufficient to cause said adverse effects associated with the administration of racemic felodipine.

20 In addition, the present invention encompasses an antianginal composition for the treatment of a human having angina, which comprises an amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its
25 R(+) stereoisomer, said amount being sufficient to alleviate said angina but insufficient to cause adverse effects of racemic felodipine.

A further aspect of the present invention includes a method of treating a condition caused by
30 excessive calcium influx in cells in a human, while avoiding the concomitant liability of adverse effects, which comprises administering to said human in need of a reduction in excessive calcium influx an amount of S(-) felodipine, or a pharmaceutically acceptable salt
35 thereof, substantially free of its R(+) stereoisomer,

- 16 -

sufficient to alleviate said condition but
insufficient to cause the adverse effects associated
with the administration of racemic felodipine.
Conditions caused by excessive calcium influx in cells
5 in a human include but are not limited to cerebral
ischemia, cerebral disorders such as cognitive
disorders including but not limited to Alzheimer's
dementia and memory impairment, arrhythmias, cardiac
hypertrophy, congestive heart failure, coronary
10 vasospasm, migraine, bronchospasm and asthma,
Raynaud's phenomenon, myocardial infarction, renal
impairment and acute renal failure.

Furthermore, the present invention includes
a composition for treating a condition caused by
15 excessive calcium influx in cells in a human, which
comprises an amount of S(-) felodipine, or a
pharmaceutically acceptable salt thereof,
substantially free of its R(+) stereoisomer, said
amount being sufficient to alleviate said condition
20 but insufficient to cause the adverse effects
associated with the administration of racemic
felodipine.

The commercially available racemic mixture
of felodipine (e.g., a 1:1 racemic mixture of the two
25 enantiomers) causes antihypertensive and antianginal
activity; however, this racemic mixture, while
offering the expectation of efficacy, causes adverse
effects. Utilizing the S(-) isomer of felodipine
results in clearer dose-related definitions of
30 efficacy, surprisingly diminished adverse effects, and
accordingly, an improved therapeutic index. It is,
therefore, more desirable to use the S(-) isomer of
felodipine.

The term "adverse effects" includes, but is
35 not limited to, cardiovascular effects (including

- 17 -

tachycardia and diminished contractility of the heart), edema of the extremities, headache, dizziness, flushing, fatigue, vertigo, and muscle cramps.

The term "substantially free of its R(+)

5 stereoisomer" as used herein means that the composition contains a greater proportion or percentage of the S(-) isomer of felodipine in relation to the R(+) isomer of felodipine, the percentages being based on the total amount of
10 felodipine. In a preferred embodiment the term "substantially free of its R(+) stereoisomer means that the composition contains at least 90% by weight of S(-) felodipine, and 10% by weight or less of R(+) felodipine. In the most preferred embodiment the term
15 "substantially free of the R(+) stereoisomer" means that the composition contains at least 99% by weight S(-) felodipine, and 1% or less of R(+) felodipine. In another preferred embodiment the term "substantially free of its R(+) stereoisomer" as used
20 herein means that the composition contains 100% by weight of S(-) felodipine. The terms "substantially optically pure S(-) isomer of felodipine" and "optically pure S(-) isomer of felodipine" are also encompassed by the above-described meanings.

25 The term "treating hypertension" as used herein means providing a normalization to otherwise elevated systolic and/or diastolic blood pressure, and by so doing providing relief from any possible symptoms or other hemodynamic effects caused by the
30 elevated pressure.

The term "a method of treating angina" as used herein means relief from the symptoms of myocardial ischemia, which include, but are not limited to, episodes of precordial pressure,
35 discomfort, or a severe intense, crushing pain which

may radiate, and which may be accompanied by changes in respiration, pulse rate, and blood pressure.

The term "a condition caused by excessive calcium influx in cells in a human" includes but is not limited to conditions involving calcium influx into a human cell that may be present in smooth muscle, cardiac, and other tissues including lung and brain. These conditions include, but are not limited to, cerebral ischemia, cerebral disorders such as cognitive disorders including Alzheimer's dementia and memory impairment, arrhythmias, cardiac hypertrophy, congestive heart failure, coronary vasospasm, migraine, bronchospasm and asthma, Raynaud's phenomenon, myocardial infarction, renal impairment and acute renal failure. The symptoms associated with these disorders include, but are not limited to, the symptoms of precordial discomfort or pain, headache, fatigue, decreased exercise tolerance, syncope, shortness of breath, nausea, lightheadedness, edema, pulmonary congestion, arrhythmia or palpitation, azotemia, and/or oliguria.

The preparation of optically pure S(-) felodipine can be accomplished by the methods disclosed in Lamm, B., and Simonsson, R., *Tett. Letters*, 30(46): 6423-6426 (1989) which is hereby incorporated by reference and Eltze, M. *et. al. Chirality* 2:233 (1990).

The magnitude of a prophylactic or therapeutic dose of (-) felodipine in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the

conditions described herein, is from about 0.01 mg. to about 100.0 mg. Preferably, a daily dose range should be between about 0.5 mg to about 20.0 mg. while most preferably, a daily dose range should be between about 0.5 mg to about 10 mg. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 0.025 mg to about 2.5 mg and increased up to about 20 mg or higher depending on the patient's global response. It is further recommended that children and patients over 65 years, and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on global response and blood level. It may be necessary to use dosages outside these ranges in some cases.

The various terms, "an amount sufficient to alleviate hypertension but insufficient to cause said adverse effects, "an amount sufficient to alleviate said condition but insufficient to cause said adverse effects" wherein said condition is angina; and "an amount sufficient to alleviate said condition but insufficient to cause said adverse effects" wherein said condition includes but is not limited to cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, coronary vasospasm, myocardial infarction, renal impairment and acute renal failure are encompassed by the above described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of S(-) felodipine. For example, oral, rectal, parenteral, transdermal, subcutaneous, intramuscular, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise S(-) felodipine as active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Such acids include acetic, benzene-sulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like. Particularly preferred are besylate, hydrobromic, hydrochloric, phosphoric and sulfuric acids. (See Campbell, S.F. et al., US 4,806,557.)

The compositions include compositions suitable for oral, rectal and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form, and prepared by any of the methods well known in the art of pharmacy.

In the case where an oral composition is employed, a suitable dosage range for use is from

- 21 -

about 0.01 mg. to about 100.0 mg. total daily dose, given as a once daily administration in divided doses such as twice daily, if required. In one embodiment of the present invention S(-) felodipine is given by
5 tablet twice daily or as a sustained-release formulation which allows once-a-day dosage schedule. Preferably, a dose range of between about 0.5 mg to about 20.0 mg is given as a once daily administration or in divided doses if required, and most preferably a
10 dose range of from between about 0.5 mg to about 10.0 mg is given as a once daily administration or in divided doses if required. Patients may be upward titrated from below to within this dose range to a satisfactory control of symptoms or blood pressure as
15 appropriate.

In practical use, S(-) felodipine can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques.
20 The carrier may take a wide variety of forms depending on the form of the preparation desired for administration, e.g., oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form any of the usual
25 pharmaceutical media may be employed. Usual pharmaceutical media include, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example,
30 suspensions, solutions, and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example,
35 powders, capsules, and tablets) with the oral solid

- 22 -

preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release and sustained release means and/or delivery devices such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; EPA 0274176; EPA 0317780; 5,015,479; and 4,803,031 the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosols sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if

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necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, and/or surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 0.01 mg to about 50 mg of the active ingredient, and each cachet or capsule contains from about 0.5 mg to about 50 mg of the active ingredient, S(-) felodipine. Most preferably, the tablet, cachet or capsule contains either one of three dosages, 0.5 mg, 2.5 mg and 5.0 mg (as scored tablets, the preferable dose form) of the active ingredient.

The invention is further defined by reference to the following examples describing in detail the testing and preparation of the compositions of the present invention. It will be apparent to those skilled in the art, that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

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4. EXAMPLES

4.1. EXAMPLE 1

Vascular Selectivity Studies

The relative potency of optically pure S(-) felodipine and racemic felodipine as calcium channel antagonists and negative inotropic agents are

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determined by a pharmacological study. Evaluation of these compounds and others in *in vitro* test systems provide results, from which the vascular selectivity of a particular compound can be assessed. Calcium channel antagonist activity of the compounds as a function of their molar concentration can be evaluated by measuring their inhibition of the calcium-induced contraction of strips of rat aorta immersed in a bath of Krebs-Henseleit buffer containing 45mM K⁺ and no Ca²⁺. In the presence of various concentrations of the antagonists, inhibition would occur in the contraction of this isolated tissue preparation in response to the addition of calcium chloride. Antagonists may be compared by examining the molar concentration of compounds inhibiting the calcium-induced contraction by 50%.

As an index of cardiac depression, negative inotropic activity may be comparably assessed using isolated heart preparations of adult rats. The tissues are prepared and perfused *in vitro* with Krebs-Henseleit buffer solution, with the activity of the calcium channel antagonists evaluated as a function of their concentration. The compounds are tested for their ability to alter cardiac contraction. Relative potency is calculated from the IC₂₅ values of the compounds, *i.e.*, the concentration required to depress contraction by 25%.

4.2. EXAMPLE 2

30 Radioligand Binding Studies

Hind limb skeletal muscles from rats or guinea pigs are minced and homogenized. After filtration and repeated centrifugation, the pellet is homogenized and diluted in a Tris buffer to a protein concentration of 1-3 mg/ml. Volumes of this

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suspension containing 3-10 μ g protein are incubated in the presence of a fixed concentration of 0.2 to 0.5 nM (+)-[3 H]-isradipine or a similar radioactive ligand and increasing concentrations of racemic felodipine, S(-) felodipine or R(+) felodipine. After 1 hour incubation, the bound and free radioactivity is measured in a scintillation counter and the affinity of the test compounds to the receptors is calculated.

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4.3. EXAMPLE 3Effects on Coronary Vascular Resistance
in the Guinea Pig Langendorff Heart Preparation

Male guinea pigs weighing between 400 and 450 g are killed by cervical dislocation. The hearts are removed and perfused with Krebs-Henseleit solution at constant pressure (60 cm water) by means of retrograde cannulation of the aorta in a Langendorff apparatus. The Krebs-Henseleit solution, consisting of 118.0 mM NaCl, 4.7 mM KCl, 5.5 mM CaCl_2 , 1.2 mM MgSO_4 , 25.0 mM NaHCO_3 , and 5.0 mM glucose, is prewarmed to 37° C and gassed with a mixture of 95% oxygen/5% carbon dioxide. A balloon catheter connected to a pressure transducer is placed in the left ventricle via the left atrium and is preloaded to a pressure of 40 mm Hg. Coronary perfusate flow is measured continuously, and changes in heart rate and left ventricular contractility are also monitored continuously.

Each experiment consists of a 30 minute equilibrium period during which coronary flow is stabilized at 9-12 ml/min. Following this period, a vasoconstrictor is injected 3 times at 40 minute intervals into the cannulated aorta. This dose of U-46619 (9,11-methanoepoxy-PGH $_2$) evokes approximately a 75% decrease in coronary flow within 30-40 sec, and the effect is fully reversible after 20-25 min

continuous perfusion. Racemic felodipine, S(-) felodipine or R(+) felodipine dissolved in dimethyl sulfoxide or the vehicle are injected in increasing concentrations prior to further U-46619 injections.

5 The mean decrease in coronary flow obtained with three consecutive injections of U-46619 in the absence of the test substance is taken to be 100% and the percent inhibition of this effect in the presence of increasing concentrations of the test drugs is
10 calculated. Complete individual dose-response curves for each test drug are generated in five hearts, enabling the calculation of the dose for the half-maximal antivasoconstrictor effect (ID₅₀).

15 4.4. EXAMPLE 4

 Antihypertensive Efficacy in
 Spontaneously Hypertensive Rats

 Male spontaneously hypertensive rats (300-350 g) are anesthetized, and polyethylene catheters
20 are implanted in the abdominal aorta via a femoral artery, and in the abdominal vena cava via a femoral vein. The arterial catheters are connected to pressure transducers by means of an intraflow device, flushing the catheters with 3 ml/hr. Mean arterial
25 pressures are derived electronically from the blood pressure wave. Mean pretreatment values of mean arterial pressure are in the range of 160-220 mm Hg. Doses of racemic felodipine, S(-) felodipine and R(+) felodipine, or of the solvent vehicle, are injected
30 into the venous catheter. Responses in mean arterial pressure to the respective drug or solvent are registered and the relative potencies of the test compounds are calculated.

- 27 -

4.5. EXAMPLE 5Cardiovascular

Calcium Antagonism, Guinea Pig Ileum (*in vitro*):

- Test substance (3 $\mu\text{g/ml}$) inhibition of the
 5 contractile response of the K^+ -depolarized isolated
 guinea pig ileal segment, bathed in Ca-free
 physiological salt solution at 37° C, to added calcium
 (20 $\mu\text{g/ml}$ of CaCl_2), indicates calcium antagonist
 activity.

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Reference Agents (ED_{100} , $\mu\text{g/ml}$):

15	atropine	>2	isoxuprine	4
	cinnazirizine	1	mepyramine	>5
	cyproheptadine	0.025	nifedipine	0.001
20	diltiazem	0.01	papaverine	4
	diphenhydramine	1	promethazine	0.25
	flunarizine	0.1	propranolol	4
	ipratropium bromide	>2	verapamil	0.01

4.6. EXAMPLE 6

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Studies on Insulin Resistance

- Insulin is a hormone that activates various
 biochemical processes in the body, the most well known
 being facilitation of glucose transport over cell
 membranes and activation of cell growth. The
 30 development of insulin resistance is common both in
 diabetics and nondiabetics, but it is only the glucose
 transport system that develops resistance to insulin.
 To compensate for the impaired glucose transport, the
 normal body produces more insulin and the diabetic
 35 patient has to inject higher doses of insulin. Since

insulin also is a growth hormone, the increased insulin concentration induces an accelerated growth of atherosclerotic lesions and increased risk for cardiovascular morbidity and mortality.

5 The present studies are performed in old, spontaneously hypertensive rats (SHRs), which are known to develop insulin resistance. Racemic felodipine, S(-) felodipine, and R(+) felodipine are studied for their effects on glucose transport,
10 insulin plasma concentration and arterial blood pressure.

Prior to receiving vehicle or test compound, basal measurements of the following parameters are made: (1) systolic blood pressure (measured via tail
15 cuff occlusion); (2) fasting levels of plasma insulin and triglycerides; and (3) glucose tolerance.

The SHRs receive vehicle or test compound via oral gavage once or twice daily for two or four weeks. Measurements of blood pressure, circulating
20 insulin and triglycerides, and glucose clearance are made following two (and four) weeks of drug administration. Any changes in insulin resistance resulting from the drug treatment are evident as changes in the ratio of plasma glucose/plasma insulin
25 levels and from the glucose tolerance tests.

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4.7. EXAMPLE 7
ORAL FORMULATION

Capsules:

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	Formula	Quantity per capsule in mg.		
		<u>A</u>	<u>B</u>	<u>C</u>
10	Active ingredient S(-) Felodipine	0.5	2.5	5.0
	Lactose	83.5	81.5	79.0
	Corn Starch	15.0	15.0	15.0
	Magnesium Stearate	1.0	1.0	1.0
	Compression Weight	100.0	100.0	100.0

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The active ingredient, S(-) felodipine, lactose, and corn starch are blended until uniform; then the magnesium stearate is blended into the resulting powder. The resulting mixture is
20 encapsulated into suitably sized two-piece hard gelatin capsules.

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4.8. EXAMPLE 8
ORAL FORMULATION

Tablets

5	Formula	Quantity per Tablet in Gm.		
		A	B	C
	Active ingredient, S(-)felodipine	0.5	2.5	5.0
10	lactose BP	183.0	181.0	178.5
	starch BP	15.0	15.0	15.0
	Pregelatinized Maize Starch BP			
	magnesium stearate	1.5	1.5	1.5
	Compression Weight	200.0	200.0	200.0

15 The active ingredient, S(-) felodipine, is
sieved through a suitable sieve and blended with
lactose, starch, and pregelatinized maize starch.
Suitable volumes of purified water are added and the
20 powders are granulated. After drying, the granules
are screened and blended with the magnesium stearate.
The granules are then compressed into tablets using 7
mm diameter of punches.

25 Tablets of other strengths may be prepared
by altering the ratio of active ingredient to lactose
or the compression weight and using punches to suit.

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- 31 -

What is claimed is:

1. A method of treating hypertension in a human while avoiding the concomitant liability of adverse effects associated with administration of
5 racemic felodipine, which comprises administering to said human in need of antihypertensive therapy, an amount of S(-)felodipine, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to
10 alleviate said hypertension but insufficient to cause said adverse effects of racemic felodipine.
2. The method of claim 1 wherein S(-) felodipine is administered by intravenous infusion, by transdermal delivery, or orally as a tablet or a
15 capsule.
3. The method of claim 2 wherein the amount administered is from about 0.01 mg to about 100.0 mg daily.
4. The method of claim 3 wherein the
20 amount administered is from about 0.5 mg to about 20 mg.
5. The method of claim 4 wherein the amount administered is from about 0.5 mg to about 10.0 mg.
- 25 6. The method of claim 1 wherein the amount of S(-) felodipine or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of felodipine.
7. The method of claim 1 wherein the
30 amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

8. The method according to claims 2, 3, 4, 5, or 6, wherein S(-) felodipine is administered as a besylate salt.

9. An antihypertensive composition for the treatment of a human in need of antihypertensive therapy which comprises, an amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said hypertension, but insufficient to cause adverse effects associated with the administration of racemic felodipine.

10. A composition according to claim 9 wherein the amount is about 0.01 mg to about 100.0 mg.

11. A composition according to claim 10 wherein said composition is administered from one to four times a day.

12. A composition according to claim 11 wherein said composition is administered once a day.

13. A composition according to claim 10 which comprises S(-) felodipine besylate.

14. A composition according to claim 13 wherein said composition is adapted for oral administration.

15. A composition according to claim 13 adapted for intravenous delivery.

16. A composition according to claim 13 for use in a transdermal formulation.

17. A composition according to claim 16 for use as a transdermal patch.

18. The composition according to claim 9 wherein S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

19. A method of treating angina in a human, while avoiding the concomitant liability of adverse effects associated with administration of racemic felodipine, which comprises administering to said
5 human in need of such anti-angina therapy an amount of S(-) felodipine, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said angina but insufficient to cause said adverse effects
10 associated with the administration of racemic felodipine.

20. The method of claim 19 wherein S(-) felodipine is administered by intravenous infusion, by transdermal delivery, or orally as a tablet or a
15 capsule.

21. The method of claim 20 wherein the amount administered is from about 0.01 mg to about 100.0 mg.

22. The method of claim 21 wherein the
20 amount administered is from about 0.5 mg to about 20.0 mg.

23. The method of claim 22 wherein the amount administered is from about 0.5 mg to about 10.0 mg.

24. The method of claim 19 wherein the
25 amount of S(-) felodipine or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of felodipine.

25. The method of claim 19 wherein the
30 amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

26. The method according to claims 20, 21, 22, 23 or 24 wherein S(-) felodipine is administered as a besylate salt.

27. An antianginal composition for the treatment of a human having angina which comprises, an amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said angina but insufficient to cause adverse effects of racemic felodipine.

28. A composition according to claim 27 wherein the amount is about 0.01 mg to about 100.0 mg.

29. A composition according to claim 28 wherein said composition is administered from one to four times a day.

30. A composition according to claim 29 wherein said composition is administered once a day.

31. A composition according to claim 28 which comprises S(-) felodipine besylate.

32. A composition according to claim 31 wherein said composition is adapted for oral administration.

33. A composition according to claim 31 adapted for intravenous delivery.

34. A composition according to claim 31 for use in a transdermal formulation.

35. A composition according to claim 34 for use as a transdermal patch.

36. The composition according to claim 27 wherein S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

37. A method of treating a condition caused by excessive calcium influx in cells in a human, while

avoiding the concomitant liability of adverse effects associated with administration of racemic felodipine, which comprises administering to said human in need of such therapy, an amount of S(-) felodipine, or a
5 pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said condition but insufficient to cause said adverse effects associated with the administration of racemic
10 felodipine.

38. The method according to claim 37 wherein said condition caused by excessive calcium influx in cells in a human is selected from the group consisting of cerebral ischemia, cerebral disorders,
15 cognitive disorders, Alzheimer's dementia, memory impairment, arrhythmias, cardiac hypertrophy, congestive heart failure, coronary vasospasm, migraine, bronchospasm and asthma, Raynaud's phenomenon, myocardial infarction, renal impairment
20 and acute renal failure.

39. The method of claim 37 wherein S(-) felodipine is administered by intravenous infusion, by transdermal delivery, or orally as a tablet or a capsule.

25 40. The method of claim 39 wherein the amount administered is from about 0.01 mg to about 100.0 mg.

41. The method of claim 40 wherein the amount administered is from about 0.5 mg to about 20
30 mg.

42. The method of claim 41 wherein the amount administered is from about 0.5 mg to about 10.0 mg.

43. The method of claim 37, wherein the
35 amount of S(-) felodipine or a pharmaceutically

acceptable salt thereof is greater than approximately 90% by weight the total amount of felodipine.

44. The method of claim 37 wherein the amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer is administered together with a pharmaceutically acceptable carrier.

45. The method according to claim 39, 40, 41, 42 or 43, wherein S(-) felodipine besylate is administered.

46. A composition for treating a condition caused by excessive calcium influx in cells in a human which comprises an amount of S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said condition, but insufficient to cause adverse effects associated with the administration of racemic felodipine.

47. A composition according to claim 46 wherein said condition caused by excessive calcium influx in cells in a human is selected from the group consisting of cerebral ischemia, cerebral disorders, cognitive disorders, Alzheimer's dementia, memory impairment, arrhythmias, cardiac hypertrophy, congestive heart failure, coronary vasospasm, migraine, bronchospasm and asthma, Raynaud's phenomenon, myocardial infarction, renal impairment and acute renal failure.

48. A composition according to claim 46 wherein the amount is about 0.01 mg to about 100.0 mg.

49. A composition according to claim 48 wherein said composition is administered from one to four times a day.

50. A composition according to claim 49 wherein said composition is administered once a day.

- 37 -

51. A composition according to claim 48 which comprises S(-) felodipine besylate.

52. A composition according to claim 51 wherein said composition is adapted for oral administration.

53. A composition according to claim 51 adapted for intravenous delivery.

54. A composition according to claim 51 for use in a transdermal formulation.

55. A composition according to claim 54 for use as a transdermal patch.

56. The composition according to claim 46 wherein S(-) felodipine or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer is administered together with a pharmaceutically acceptable carrier.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10630**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A61K 31/44

US CL :514/356,821,826,879,929

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/356,821,826,879,929

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"The Merck Index", published 1989 by Merck & Co., Inc. (RAHWAY, NJ), #3895	1-56
Y	A.R. GENNARO, ED., "Remington's Pharmaceutical Sciences, 18th Ed.," published 1990 by Mack Publishing Co. (Easton, PA) pages 853-854.	1-56

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

"	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"A"	document member of the same patent family

Date of the actual completion of the international search

13 APRIL 1993

Date of mailing of the international search report

11 MAY 1993

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